Controversy debate 2: Selecting optimal treatments for oesophageal cancer: which patients should be operated?

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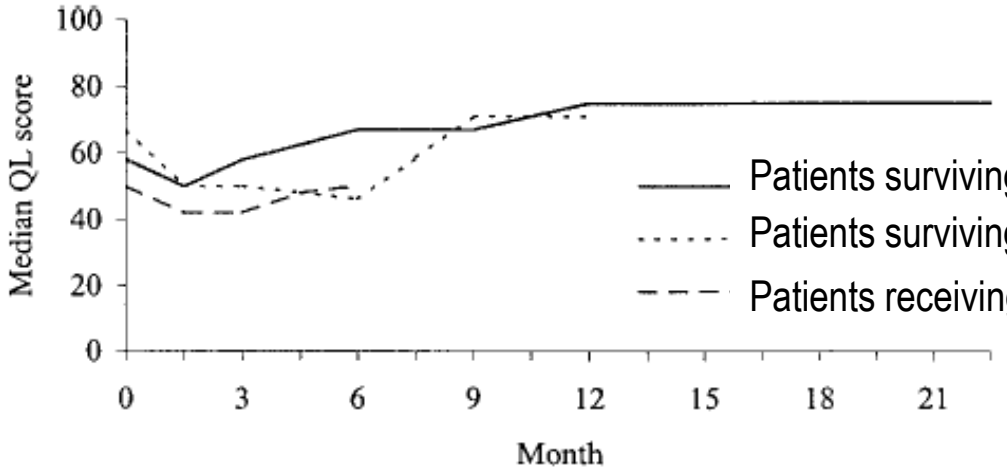
Disclosure

- *Research funding:* Amgen, AstraZeneca, Bayer, Celgene, Merck-Serono, Medimmune, Merrimack, Novartis, Roche, Sanofi

Further disclosure

Median global QoL after potentially curative oesophagectomy



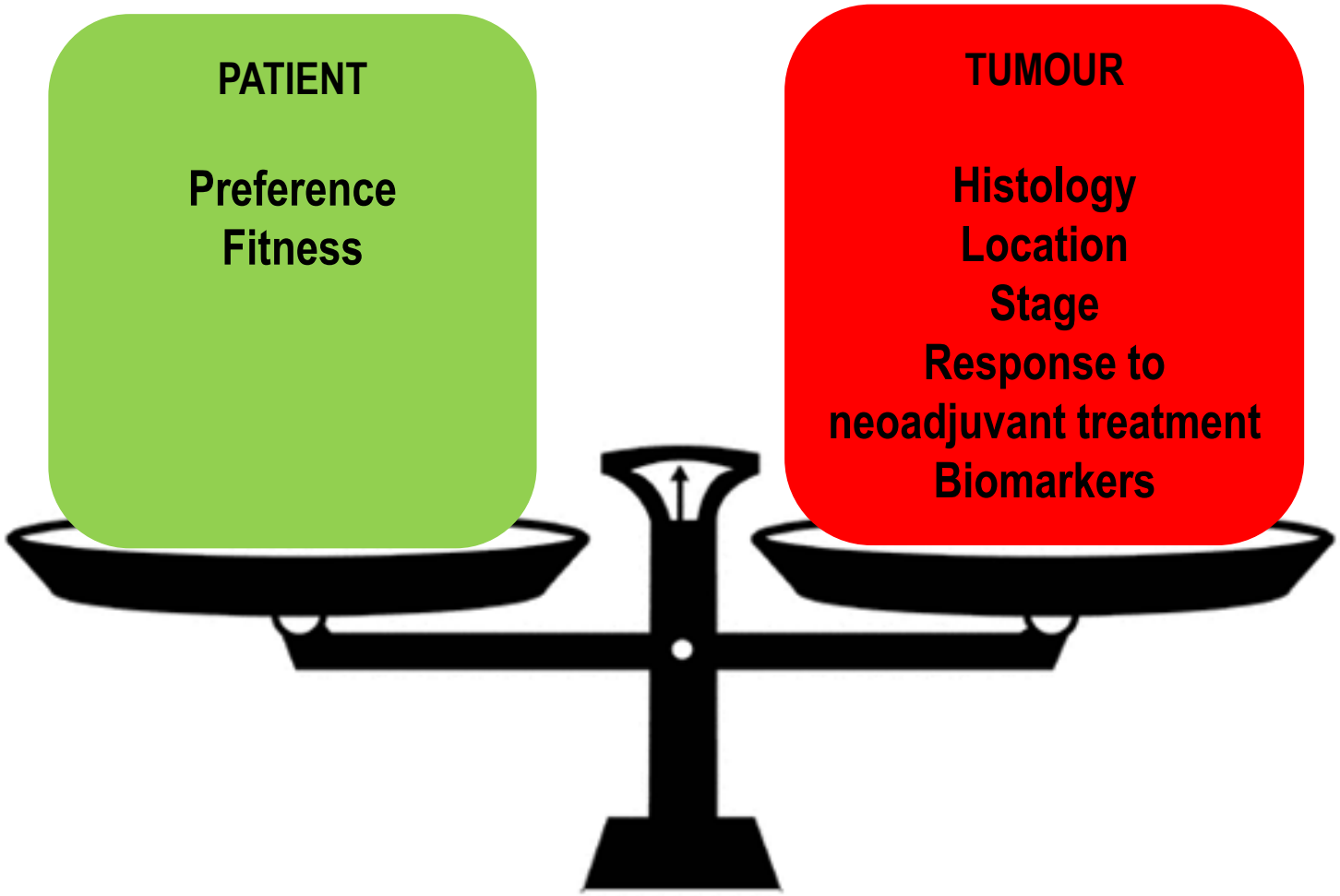
Gp 1	n	17	17	17	17	17	17	17	17
Gp 2	n	38	25	23	18	10			
Gp 3	n	37	27	13					

- > 2 years survival: QoL scores returns to pre-operative within 9 months
- < 2 years survival: QoL never returns to baseline
- Palliative setting: gradual deterioration until death

2 year survival rate for oesophageal cancer: 20 – 50%

Blazeby et al. Cancer 2000

Factors influencing decision to operate



Histology and location

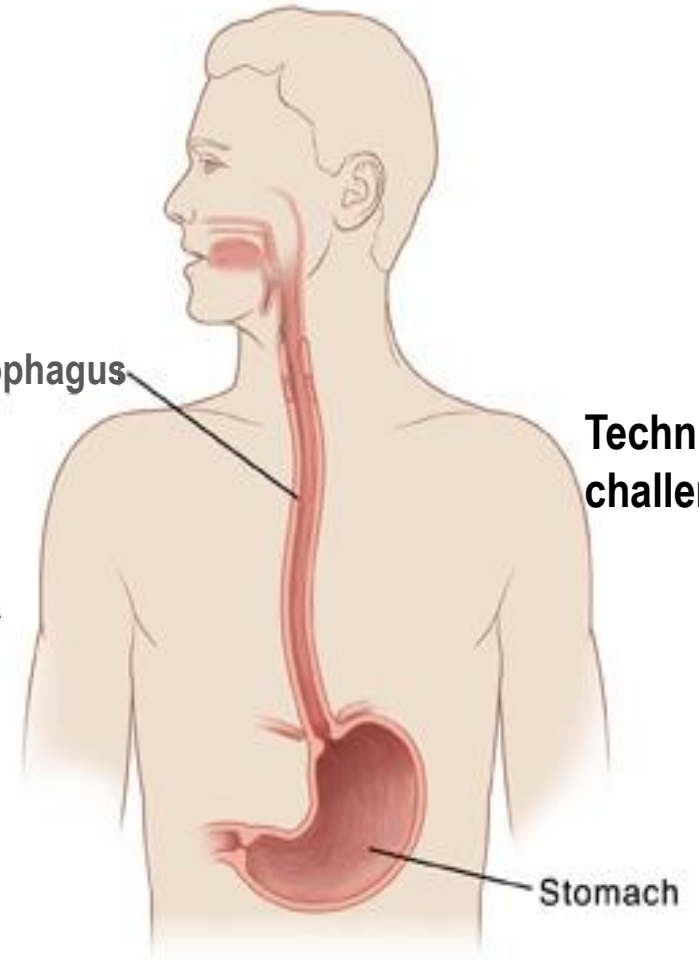
Upper third

Medium third
Lower third

Junctional
Type I
Type II
Type III

SCC

Adenocarcinoma

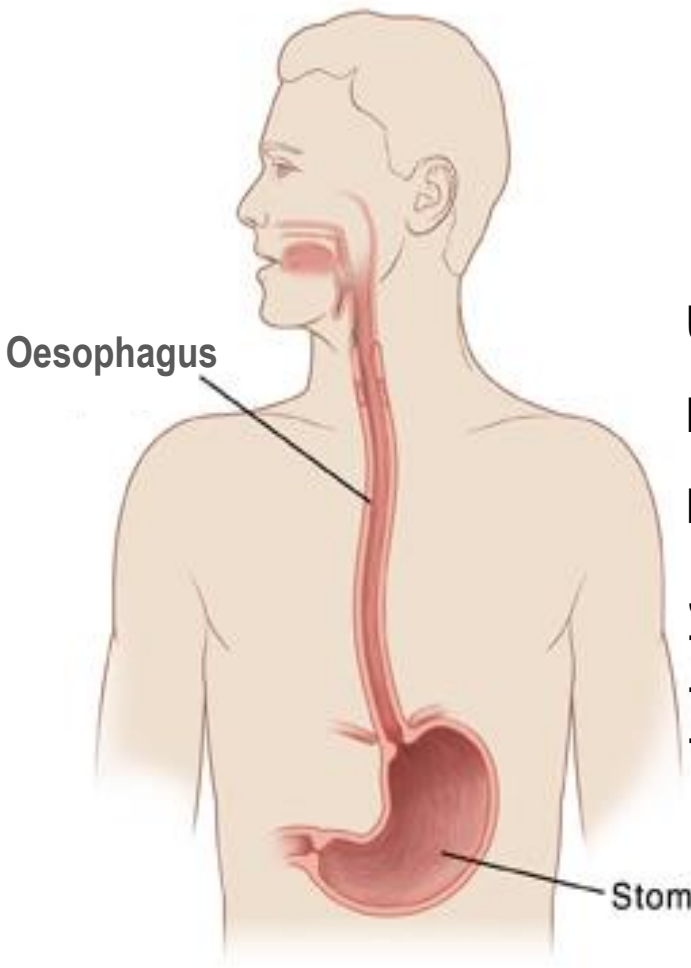


Technically challenging

Surgery

Increased morbidity

Current treatment paradigms



Definitive CRT

Neoadjuvant CT or CRT followed by surgery

Upper third

Medium third

Lower third

Junctional

Type I

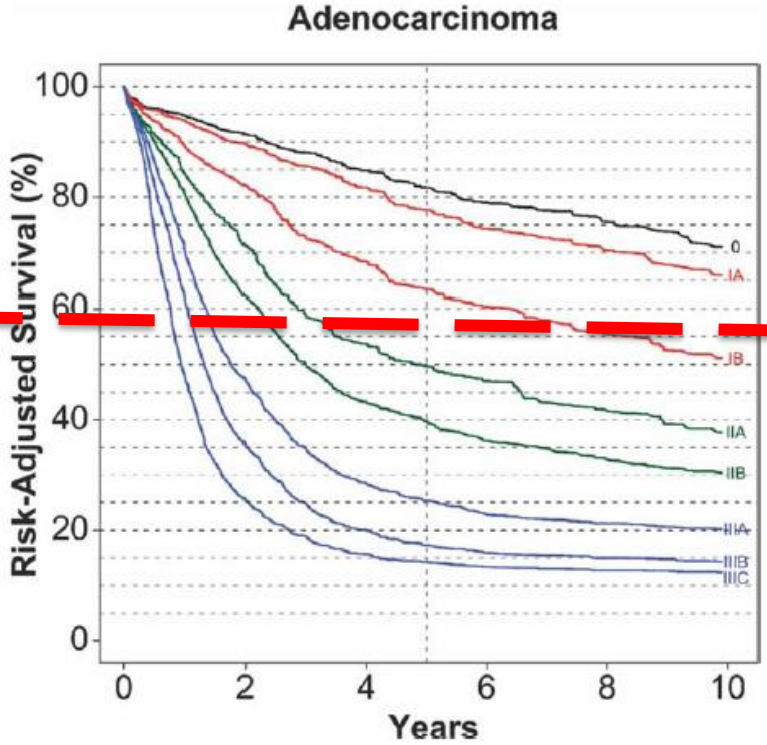
Type II

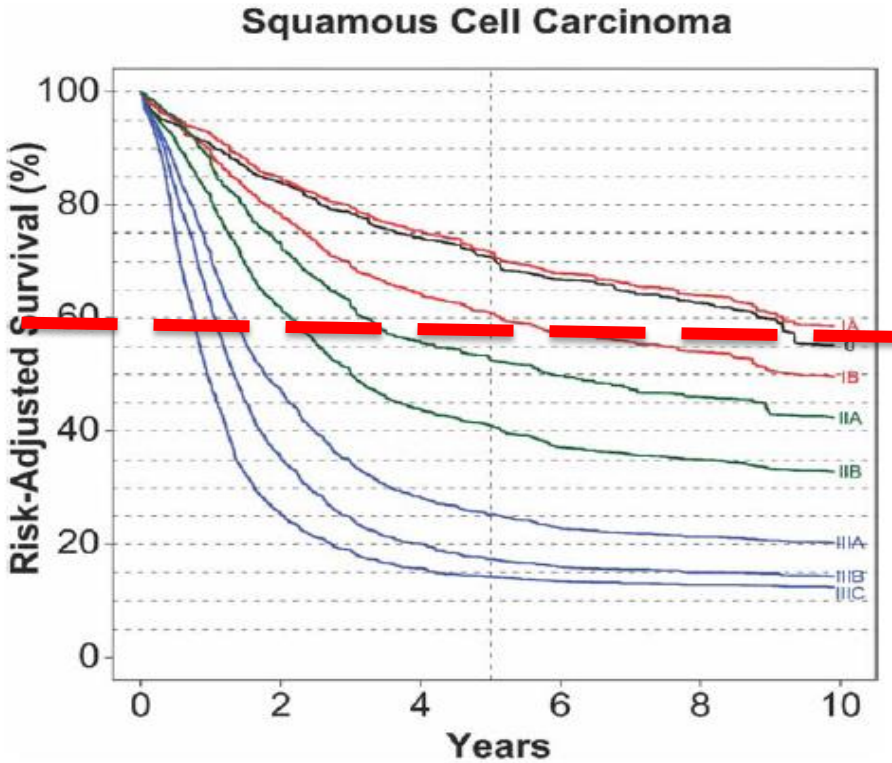
Type III

Peri-operative chemotherapy
(Surgery followed by adjuvant CT in Asian countries)

Stage

Early disease

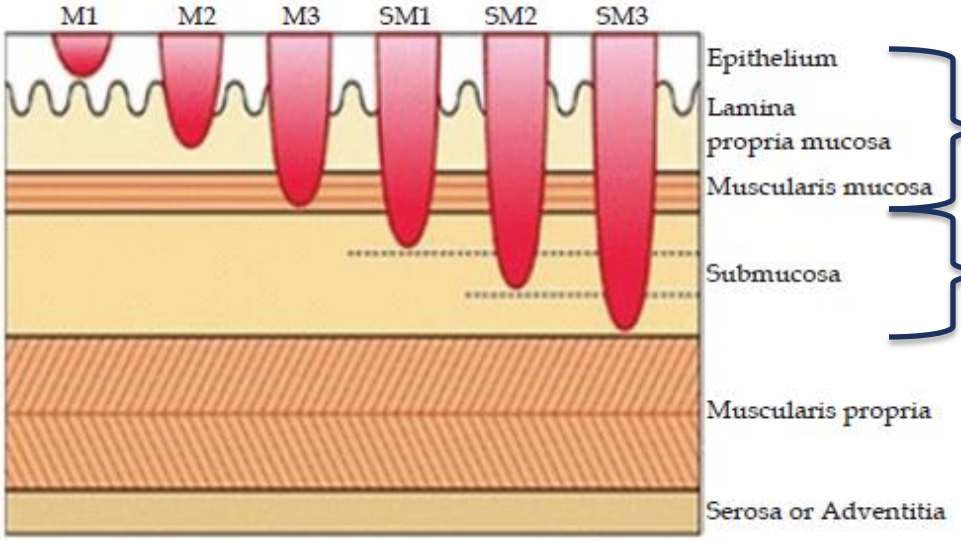




Locally advanced disease

Data-driven staging of 7th Ed. of AJCC/IUACC Staging Manual
Cancer of the Esophagus and Esophagogastric Junction. Cancer 2010;116:3763–73.

Endoscopic approach possible for early stage disease



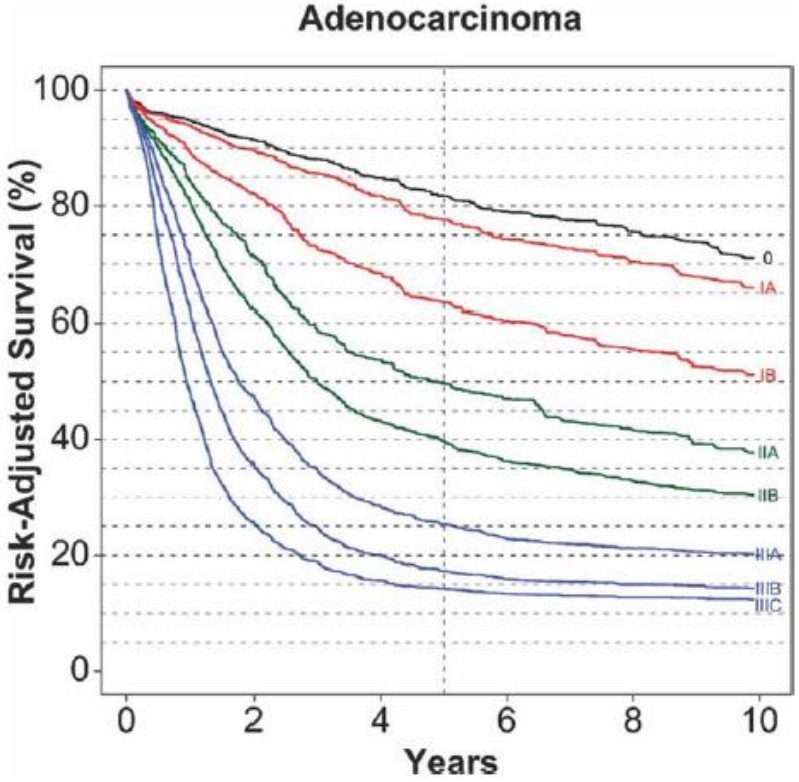
T1a:Endoscopic mucosal resection (EMR)
Risk of N + is less than 2%

T1b: Endoscopic submucosal dissection (ESD)
Risk of N+ increases from 28% for SM1 to 56% for SM3

- Accurate staging is imperative
- EUS: superior to CT for both tumour and nodal staging, but operator-dependent
- The most accurate staging is pathological ⟶ post-procedure
- Endoscopic surveillance is necessary (every 3 months for the first year, annual thereafter)

American Society of Gastrointestinal Endoscopy Guidelines 2013
Figure adapted from Eleftheriadis et al. Journal of Tumor 2014

Locally advanced disease requires multimodality approach



Decreasing benefit of surgery

Response to neoadjuvant treatment - pCR (AC vs SCC)

Trial	Arms	No. pts	AC/SCC	pCR	P
Urba et al	Surgery *vs.* CF + 45Gy	50 *vs.* 50	75/25	28% ADC 38% SCC	NA
TROG-AGTG	Surgery *vs.* CF+35Gy	128 *vs.* 128	158/95	9% ADC 27% SCC	0.02 (SCC *vs.* ADC)
CROSS	Surgery *vs.* carbo paclitaxel + 41.1Gy	188 *vs.* 178	275/84	23% ADC 49% SCC	0.0008 (SCC *vs.* ADC)

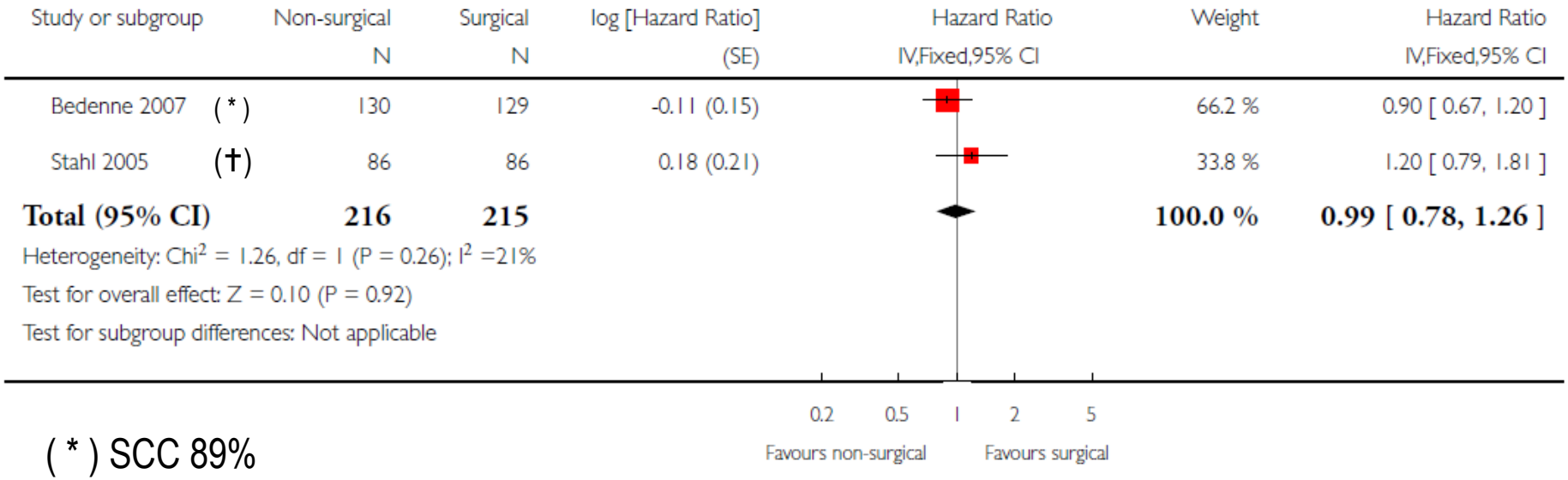
- Rates of pCR with neadjuvant CRT significantly higher for SCC across multiple studies

Response to neoadjuvant treatment - pCR (AC)

Chemotherapy Trials	Arms	No. pts	pCR	P
OE05	CF x2 *vs.* ECX x4	451 *vs.* 446	3% *vs.* 11%	NA
ST03	ECX x3+3 *vs.* ECX+Bev x3+3	533 *vs.* 530	8% *vs.* 10%	NA
Al-Batran *et al.*	ECF/ECX x3+3 *vs.* FLOTx4*4	137 *vs.* 128	5.8% *vs.* 15.6%	0.015
CRT Trials				
Burmeister *et al.*	CFx2 vs. CF→CF+30Gy	36 *vs.* 39	0% *vs.* 13%	0.02
Stahl *et al.*	PFLx2.5 vs. PLFx2 → Cis VP16 + 30Gy	59 *vs.* 60	2% *vs.* 15.6%	0.03
Ajani *et al.*	Ox 5-FU+50.4Gy *vs.* Ox 5-FUx2 → Ox 5-FU+50.4Gy	63 *vs.* 63	13% *vs.* 26%	0.094
NEOSCOPE	OxCap→ OxCap+45Gy vs. OxCap→ CarPac +45Gy	42 vs. 43	12% vs 28%	NA

- The range of pCR with chemotherapy regimens is 0-15%
  - ~3% with 2 drug regimens
  - ~10% with 3 drug regimens
- The range of pCR with chemoradiation regimens is 13-28%
  - ~14% with 30Gy regimens
  - ~27% with 45- 50Gy regimens

Role of surgery in SCC



(*) SCC 89%
(†) SCC 100%

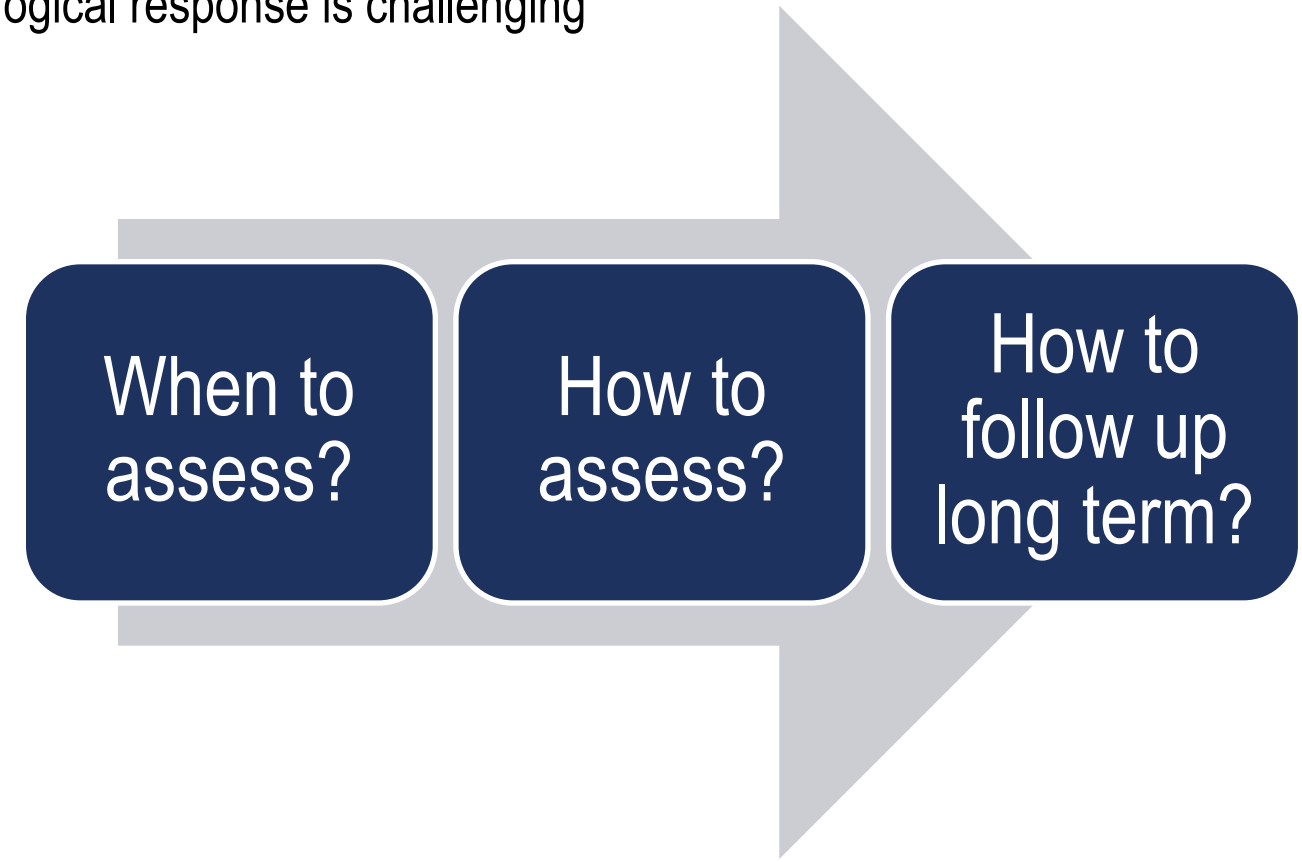
- Cochrane review 2016:

  'chemoradiotherapy appears to be at least equivalent to surgery in terms of short-term and long-term survival in people with oesophageal cancer (squamous cell carcinoma type) who are fit for surgery and are responsive to induction chemoradiotherapy'

Stahl et al. JCO 2005, Bedenne et al. JCO 2007
Cochrane database 2016: Non surgical vs surgical treatment for oesophageal cancer

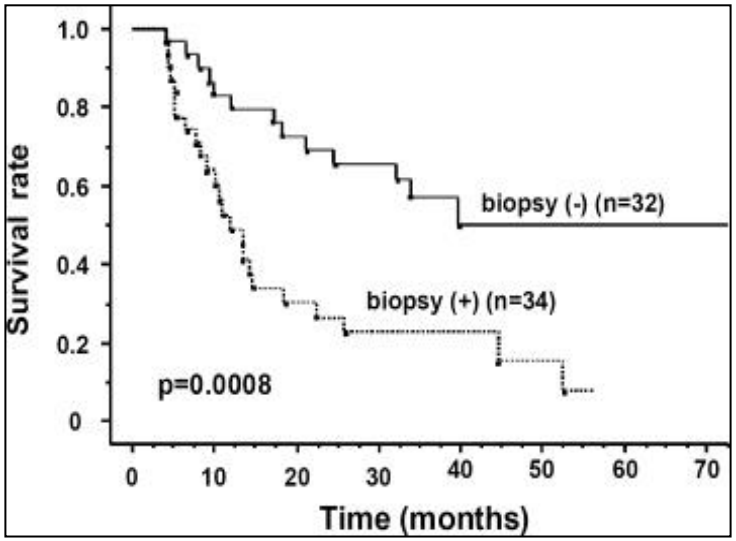
Follow up after CRT

- Treatment paradigm of definitive CRT with surgery reserved for incomplete response is dependent on reliable assessment
- In the absence of a surgical resection specimen assessment of complete pathological response is challenging



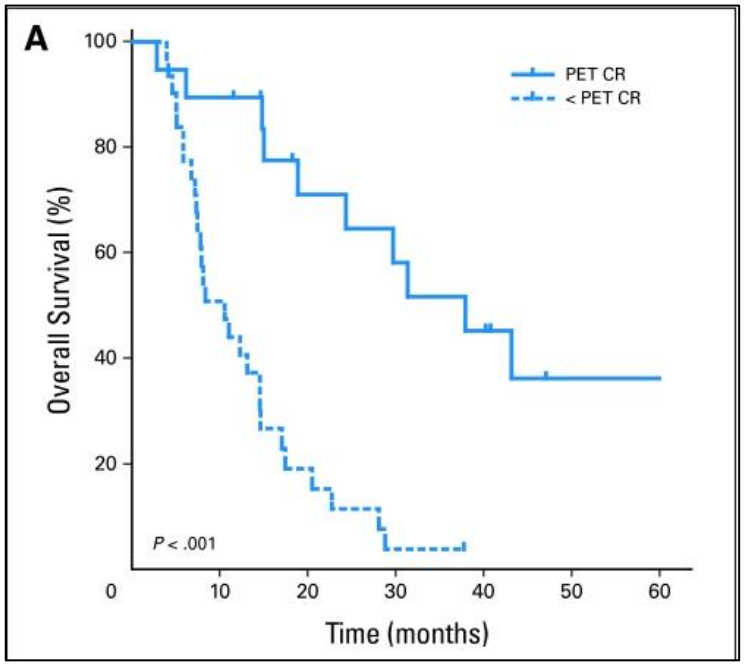
Assessing response

- Pathological response on endoscopic biopsy and metabolic response on PET predict for survival after definitive CRT



OS according to endoscopic biopsy CR at the time of 40Gy during the course of definitive CRT

Miyata et al. Prognostic Value of Endoscopic Biopsy Findings After Induction Chemoradiotherapy With and Without Surgery for Esophageal Cancer. Annals Surg. 2011; 253(2): 279–284



OS according to PET CR post definitive CRT

Monjazeb et al. Outcomes of Patients With Esophageal Cancer Staged With FDG-PET: Can Post-chemoradiotherapy FDG-PET Predict the Utility of Resection? J Clin Onc. 2010; 28(31): 4714–4721

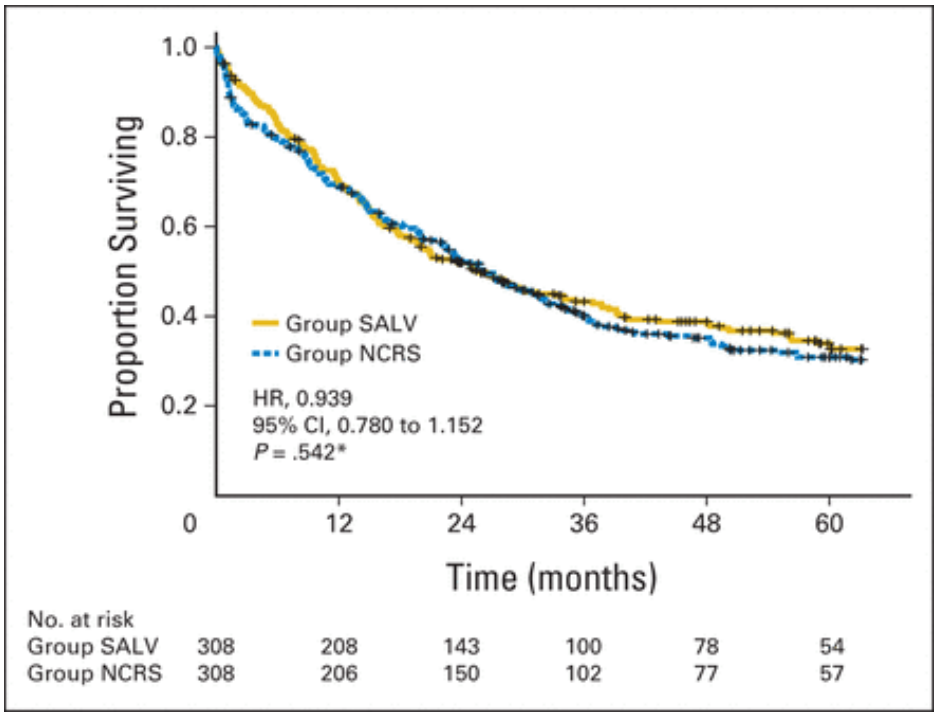
- SCOPE 1: patients had endoscopy and CT 12 weeks after completing definitive CRT
  - Patients who were failure free at 12 weeks post treatment had a significantly improved median overall survival (8.3 versus 26.7 months)

A combination of assessment modalities is necessary to further refine the concept of favourable clinical response, whereby the benefit of surgery is outweighed by its associated morbidity

Crosby et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncology. 2013: 14(7); 627-637

Salvage surgery

- Recent large case series compared definitive CRT/ salvage surgery at recurrence with neoadjuvant chemoradiotherapy/ planned surgery, with equivalent long-term outcomes



OS in propensity-matched groups: salvage oesophagectomy after definitive chemoradiotherapy (SALV) vs neoadjuvant chemoradiotherapy followed by planned oesophagectomy (NCRS)

Salvage Surgery After Chemoradiotherapy in the Management of Esophageal Cancer: Is It a Viable Therapeutic Option? Markar et al. J Clin Onc. 2015: 33(33); 3866-3873

Is there a role for non-surgical management of adenocarcinoma?

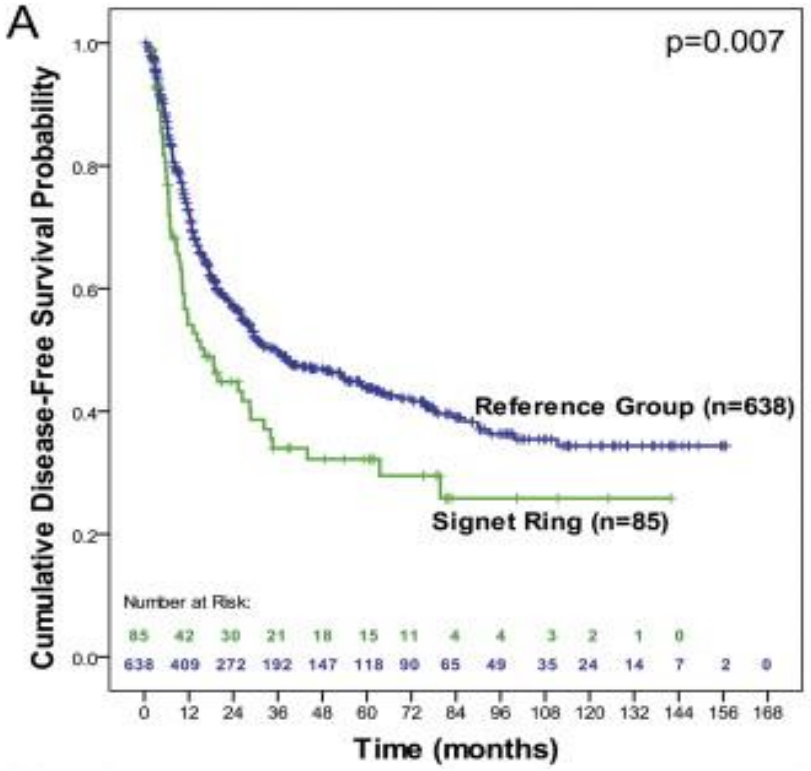
Trial	n	% SCC	2y OS %	mOS
RTOG 85-011 (1992)	61	84	38	13
Bedenne et al. (2007)	117	90	40	18
PRODIGE/ ACCORD17 (2014)	134	85	~40	20
SCOPE 1 (2016)	129	74	60	35

- Outcomes from definitive chemoradiotherapy continue to improve
- Recent long term survival results from SCOPE1 comparable to published outcomes from CRT + surgery
- Small numbers of adenocarcinoma patients included

Table adapted from ASCO presentation poster: Mukherjee et al. Long term results and patterns of recurrence from SCOPE 1: A phase II/III randomised trial of definitive chemoradiotherapy plus or minus cetuximab in esophageal cancer. J Clin Oncol 2016: 34(4s); abstr 118

Biomarkers: tumour characteristics

- Node-positive status, T3/T4 disease and presence of signet ring morphology have all been correlated with poorer outcome from CRT



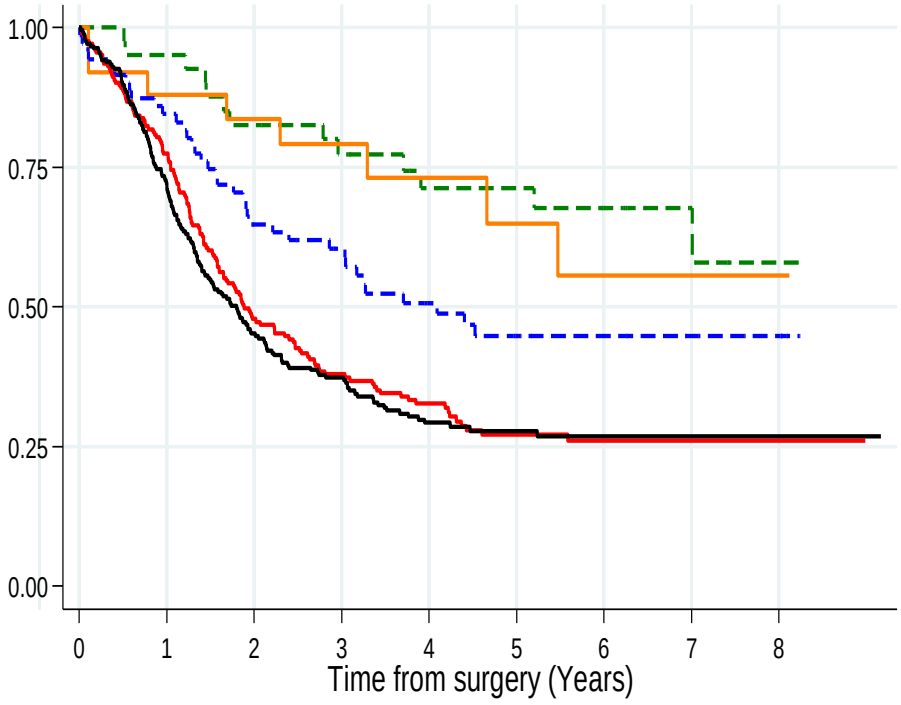
Comparison of disease-free survival after neoadjuvant CRT + surgery was significantly shorter for patients with presence of signet ring cells than for reference group of 'usual' adenocarcinoma

Patel et al. Signet Ring Cells in Esophageal Adenocarcinoma Predict Poor Response to Preoperative Chemoradiation. Annals Thor. Surg. 2014; 98(3): 1064–1071

Amini et al. Factors associated with local-regional failure after definitive chemoradiation for locally advanced esophageal cancer. Ann Surg Oncol. 2014; 21(1):306-14

Biomarkers: tumour regression grade

OEO5: Survival by TRG



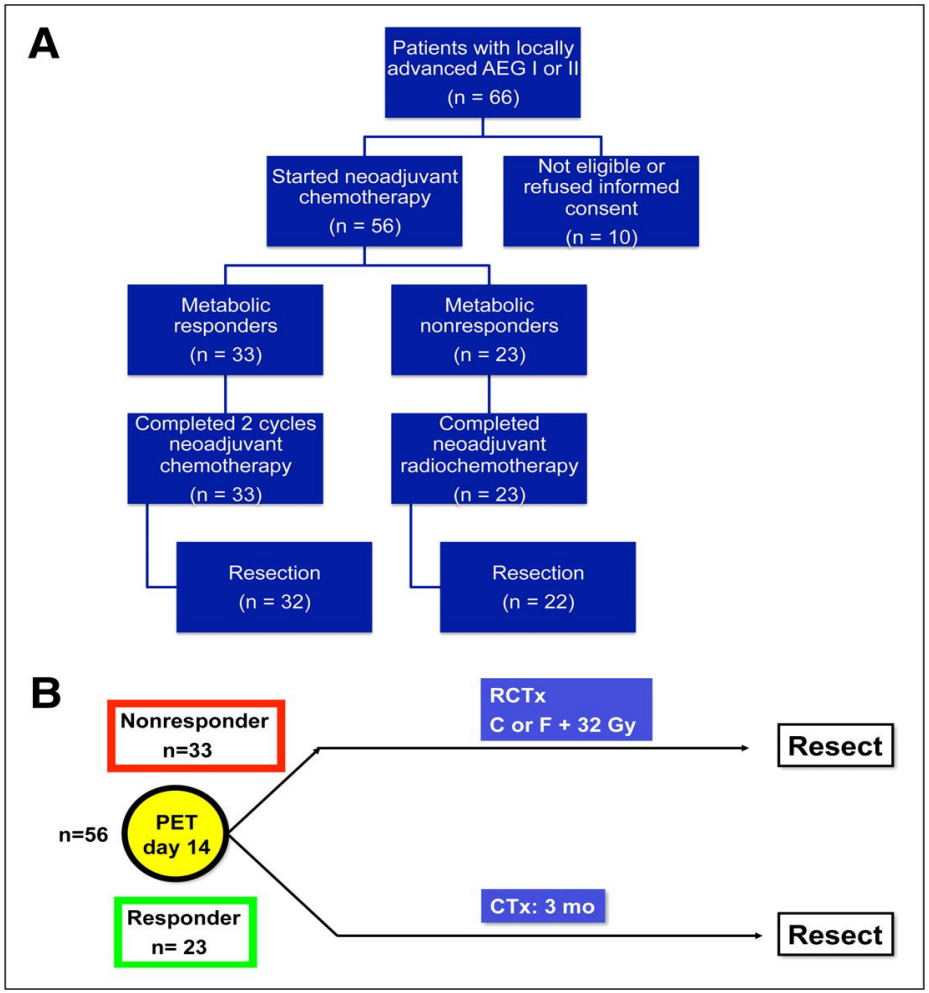
At risk									
Grade 1	41	39	33	28	23	22	15	7	1
Grade 2	25	22	19	14	10	8	4	2	1
Grade 3	71	60	45	39	29	17	13	8	5
Grade 4	204	157	97	69	45	30	23	16	9
Grade 5	243	173	108	81	47	32	22	15	6

3-year survival (95% CI)	
Grade 1-2	78% (66%, 86%)
Grade 3	60% (48%, 71%)
Grade 4-5	38% (33%, 42%)

Cunningham et al. ASCO 2015

Biomarkers: early PET response

MUNICON II



Metabolic response predicted histopathological response and survival

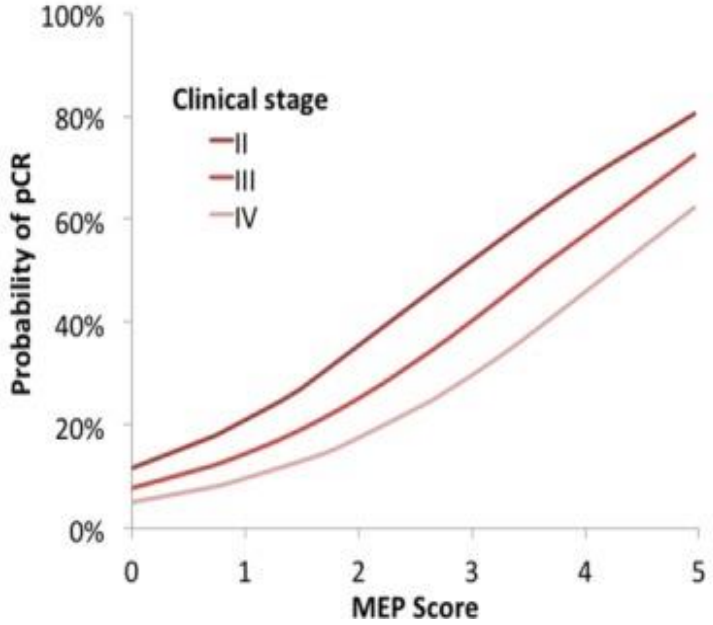
Feasibility of PET response-guided treatment algorithms

Identification of PET non-responders as poor prognostic sub-group

Lordick F, *et al*. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol . 2007; 8:797–805.

Biomarkers: gene expression analysis

- Numerous genetic biomarkers have been reported to have association with CRT response
- miRNA expression model developed to predict pCR after neoadjuvant CRT for adenocarcinoma



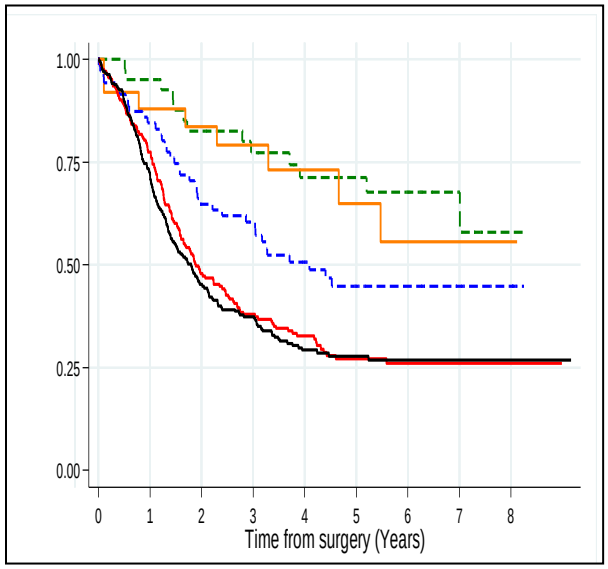
Probability of pCR increased with increasing miRNA expression profile score

Skinner et al. A validated miRNA profile predicts response to therapy in esophageal adenocarcinoma. Cancer. 2014; 120(23): 3635–3641

- As yet no candidate genetic biomarkers have been adequately validated
- Further translational work remains to be done before any such biomarker is shown to be sufficiently robust to enter routine clinical use and direct treatment decisions

Non-responders: should we operate at all?

OEO5

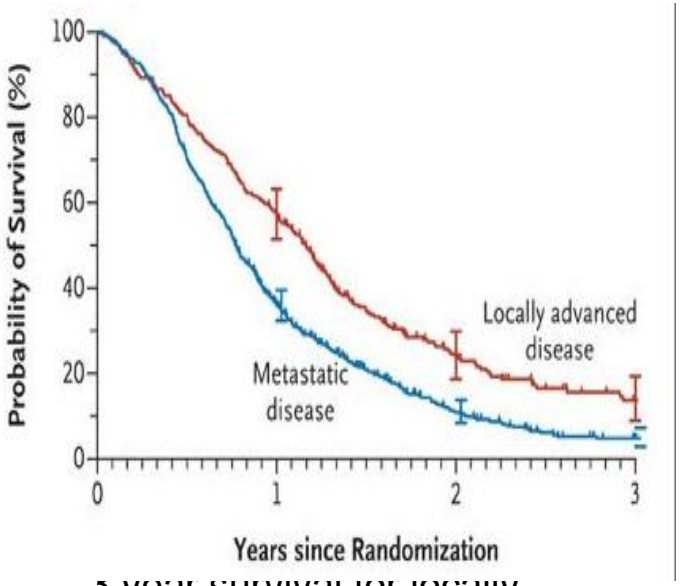


3 year survival for poorest responders who are operated:

38%

Alderson D, et al. J Clin Oncol 33, 2015 (suppl; abstr 4002)

REAL-2



3 year survival for locally advanced disease receiving palliative treatment:

~20%

Cunningham et al. N Engl J Med 2010; 362:858-859

Resectable metastatic disease

- FLOT-3: surgical resection in carefully selected 'limited' metastatic disease improves outcome compared to systemic treatment alone in gastric AC
- Schmidt et al: case series of 123 OG (70 oesophageal AC) patients with synchronous metastatic disease treated with surgery
  - For patients with clinical response to neoadjuvant treatment who then underwent successful surgery mOS reached 77 months

Possible role for surgery in carefully selected cases of metastatic disease however prospective trials to address this question will be important

A prospective trial for defining a subset of patients with limited metastatic gastric cancer who may be candidates for bimodal treatment strategies: FLOT3. J Clin Oncol. 2012; 30(suppl): abstr 4090
Surgery in oesophago-gastric cancer with metastatic disease: Treatment, prognosis and preoperative patient selection. Eur J Surg Oncol. 2015; 41(10):1340-7

Which patients should be operated?

- For surgery
  - Early node negative disease
  - Locally advanced disease not achieving pCR with neoadjuvant treatment
- Possibly not for surgery
  - Early stage Tis amenable to EMR
  - Squamous Cell Cancer
    - Definitive chemoradiation with active surveillance of those achieving pCR
  - Locally advanced adenocarcinoma achieving pCR?
    - Emerging role for CRT approaches in AC
- Not for surgery
  - Medically unfit patients or patients that decline
  - Metastatic disease (possible exceptions in few highly selected cases)